Detecting restriction using non-parametric modelling of diffusion MR data

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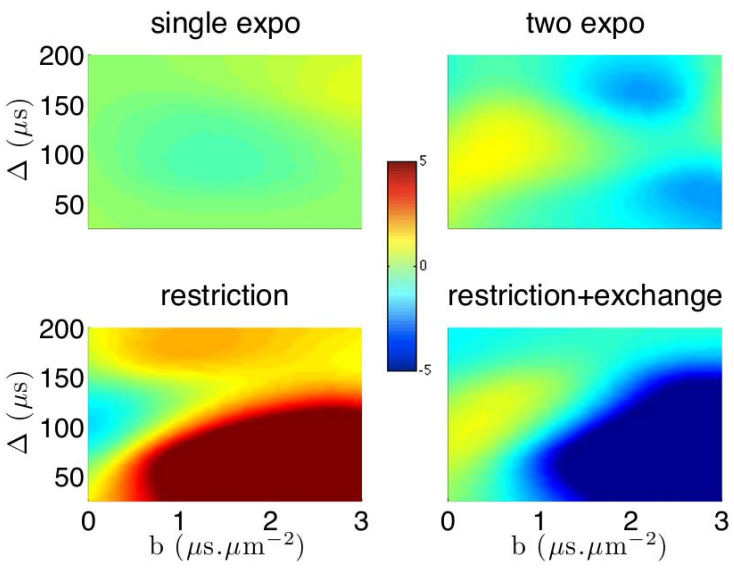
INTRODUCTION. Biophysical modelling of diffusion MR data is regaining interest amongst brain scientists [1]. At the heart of this enthusiasm is the exciting possibility of *quantifying* microstructural properties of brain tissues (e.g. axon size and density), which should have a dramatic impact on neuroscientific and/or clinical applications that rely on neuroimaging biomarkers of brain microstructure. Biophysical models that attempt to quantify microstructural features rely on specific assumptions with regards to the diffusion process. For example, in the brain white matter, *restricted* diffusion needs to be hypothesised in order to be able to relate diffusion length-scales to axonal size, and hence estimate axon size from the data.
When present in the data, restricted diffusion implies a dependence between the apparent diffusion coefficient (ADC) and the diffusion time (denoted Δ hereafter). A related qualitative indication of restriction in the data is the dependence of the signal on the b-values and the diffusion time *separately*. So far, it is not clear to what extent restriction effects are present in brain imaging data that are acquired in vivo, or in which (b,Δ) regime these effects are most prominent, an important step towards efficient experimental design. The few experiments that have explored restriction in human brain data have relied on a qualitative description of noisy data, where b and Δ have been varied independently.
Here we suggest a simple idea to (semi)-quantify the degree of restriction in noisy diffusion MR data, and present a mathematical framework that implements this idea. This framework is very generic, and may apply to the detection of other "effects" in the data, as discussed below. We proceed in three steps: (1) a qualitative description of the effect of interest on diffusion data; (2) translating this qualitative effect into a mathematical property of the signal; and (3) quantifying the effect using nonparametric modelling of the data. The outcome is a z-statistic that tells us "how much of an effect" is present in the data. Crucially, we fit a non-parametric model to the data (a Gaussian Process), which means that we do not rely on the validity of a particular biophysical model in order to interrogate the data. This framework can be used as a diagnostic tool for exploring experimental data or, if combined with an appropriate biophysical model, may be used as a tool for experimental design [2].

METHODS. In the case of restriction effects, the three steps described above are:
(1) – qualitative description: a signature of restriction in diffusion data is the dependence of the signal on the bvalue and the diffusion time separately [3].
(2) – mathematical formulation: the derivative of the signal with respect to the diffusion time (at constant bvalue) is different from zero.
(3) – statistics: by fitting a Gaussian Process to the data, we can calculate the mean and variance of the derivative defined in (2), and hence a z-statistic that tells us how much the signal, at each data point, is sensitive to restriction.
We use Gaussian Processes (GPs) for nonparametric fitting of the diffusion data. Briefly, instead of modelling an explicit dependence between the signal and the experimental parameters (b,Δ), GPs model the *covariance* between data points, then use the estimate of the covariance function to make predictions for the signal (and its derivatives) anywhere in the (b,Δ) space. These predictions include first and second order statistics (mean and variance). In summary, from a handfull of (noisy) measurements, we have a smooth representation of the data, and an estimate of the variation of the data with respect to experimental parameters. This is important because (i) estimating derivatives from noisy data is difficult, and (ii) experimental data are sparse (we only acquire a few (b,Δ) values), and hence the GP can be used for predictions at all points in the (b, Δ) plane.
We can readily see how we can use the above steps to quantify the degree of restriction from diffusion acquisitions: we fit a GP to the 2D data cloud parametrised by (b,Δ), then estimate the mean and variance of the derivative of the predicted signal with respect to Δ (at constant b), and finally use these estimates to calculate a z-statistic that we can then use to test whether the derivative is significantly different from zero, which is exactly the effect we expect in the presence of restriction.

RESULTS AND DISCUSSION. The figure below shows the results of four simulations of relatively noisy data (SNR=100) where the b-value has been varied linearly from 0 to 3 ms/µm^2 and Δ from 25 to 200 ms (20 increments each). The diffusion gradient pulse width was set to 20ms. Four different models were used: single exponential decay (constant ADC=0.8µm^2/s), two-exponentials (two compartments with ADC=0.3/3 µm^2/ms respectively), and two models of restricted diffusion as described in [4], with and without exchange between two compartments (boundary size=5µm, residence time=50ms). We can see that the z-statistics calculated using the method described above are high in a reasonably wide range of (b,Δ) for both restricted models (but not for the unrestricted ones), with an optimal (b,Δ)~(2,80) for detecting restriction effects. Note that in the case of pure restriction, the z-statistic is always positive (on average), whilst it can be either positive or negative when exchange is modelled. The sign of the z-statistic in such case depends on the biophysical model parameters (e.g. ADC and residence time) and on the range of the experimental parameters.

Analytic models for restricted diffusion are very attractive, and with the developments of MR hardware, might enable us to estimate in vivo the size of restrictive compartments at the microscopic scale. However, before fitting a complex analytic model to experimental data, it is useful to have diagnostic tools to interrogate the data for effects that are required in order for the biophysical model to be valid. Nonparametric modelling using GPs allows the data to express themselves (does not rely on the validity of a biophysical model). The framework proposed here allows us to look at the data, but goes further than a qualitative description. It can provide a whole brain voxel-wise semi-quantitative picture of an effect of interest (restriction). The idea was to turn a simple "rule of thumb" for the presence of restriction into a mathematical property of the signal, then into a statistical property using GPs. This method can be applied in other contexts, such as detecting multiple water pools (i.e. the model supporting more than one ADC value), or detecting exchange effects from data, or detecting anisotropy, etc. Any qualitative description of the signal can be turned into a mathematical property of the signal and its derivatives (with respect to the experimental parameters, not with respect to some biophysical model parameters) – and hence we can quantify these effects using Gaussian processes because they give us first and second order statistics for the signal and its derivatives.



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[3] Tanner JE, J Chem Phys 1968
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